SUPPORT FOR THE AMENDMENTS

Claim 1 has been amended.

Support for the amendment of Claim 1 is provided by original Claim 1 and serves to remove non-elected subject matter.

No new matter has been added by the present amendment.

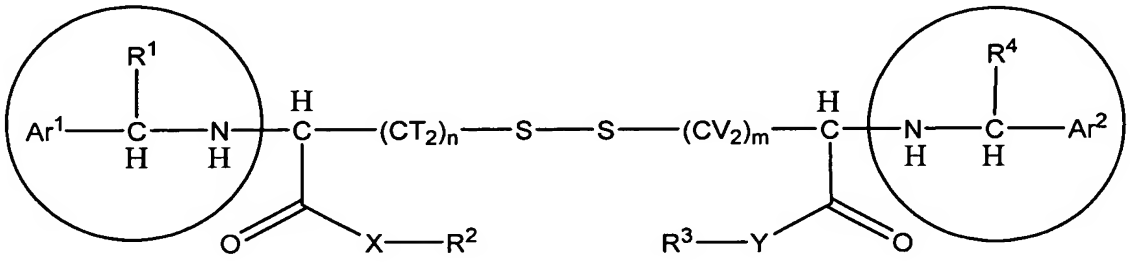
REMARKS

Claims 1-31 are pending in the present application.

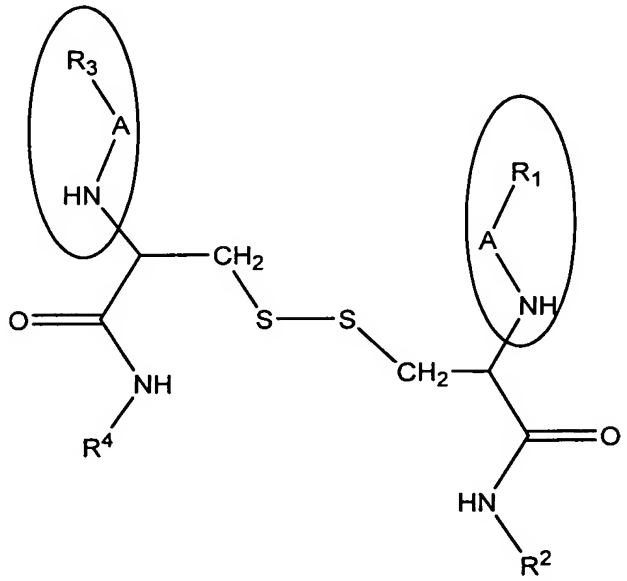
Applicants wish to thank Examiner Shiao for the helpful and courteous discussion with their undersigned Representative on December 2, 2004. During this discussion various amendments and arguments were discussed to address the rejection under 35 U.S.C. §112, second paragraph, and the rejection over the art of record. The content of this discussion is reflected by the amendments and remarks set forth herein. Reconsideration is respectfully requested.

The rejection of Claims 1-20 under 35 U.S.C. §103(a) over Grams et al (WO 00/273378) is respectfully traversed.

An important aspect of the present invention is that the substituent on the amino group of cystine derivative (*infra*) is restricted to alkyl or aryl-alkyl group to maintain the basicity as an amine.



In contrast, Grams et al disclose, several substituents on the amino group of the cystine derivative disclosed therein, which reduce the basicity of amino group such as an amide group. Specifically, the Examiner is referred to variable A of the general formula I of Grams et al (reproduced below for the Examiner's convenience):



, wherein A is a valency bond, a –CO-, -SO_2-, -NHCO-, -NHCS-, or –O-CO- group (see Abstract).

In the present invention, if Ar^1 and Ar^2 of the present compound are hydroxylaryl group, the partial structure near the amino group corresponds to hydroxyl benzyl amine moiety. On the other hand, however, if R_1 and R_3 of Grams et al are hydroxylaryl group and the variable A is -CO-, the partial structure near the amino group corresponds to hydroxyl benzoylamide moiety. These moieties (amine and amide) may be structurally similar, but have completely different properties. Therefore, the present compound is substantively distinct from that disclosed by Grams et al.

The Examiner appears to rely on the disclosure that variable A in the general formula (I) of Grams et al may be a valency bond. However, Applicants note that such a compound is not disclosed in anywhere in the specification or examples of Grams et al. Accordingly, Grams et al fail to provide motivation with sufficient specificity to select this option from the list of other alternatives. Moreover, we argued that based on the other alternatives the skilled artisan would expect that the desirable substitution on the cystine derivative would be to

decrease the basicity of the amino group and, as such, there would be no reasonable expectation of the advantages flowing from the claimed invention.

At best, the disclosure of Grams et al could be taken as an "invitation to experiment" or could be viewed as providing an "obvious to try" argument; however, "obvious to try" has long been held *not* to constitute obviousness. *In re O'Farrell*, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). The Examiner is reminded of the legal standard for supporting a proper case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation... to modify the reference... Second, there must be a reasonable expectation of success. Finally, the prior art reference... must teach or suggest all the claim limitations." (MPEP §2142) This standard is clearly not satisfied by the disclosure of Grams et al.

Further, the Examiner states that the compounds disclosed by Grams et al possess a similar activity (i.e., treating inflammatory disease) to that of the claimed compounds (see page 7, lines 13-15 of the Official Action). Apparently, this assertion is based on the disclosure of Grams et al at page 1, line 9. However, "inflammatory disease" disclosed by Grams et al means a group of diseases such as rheumatoid arthritis, in that matrix metalloproteases (MMPs) are involved (see page 1, second paragraph (ii)). As an indirect effect of these diseases, some inflammation may occurr. However, the present invention is directed to the *direct* suppression of activation of inflammatory factors. Thus, the activity of the compounds disclosed by Grams et al is completely different from that of the present invention.

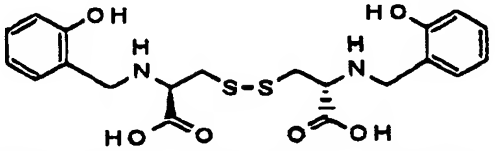
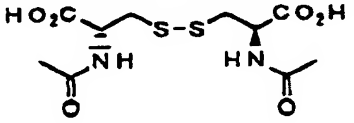
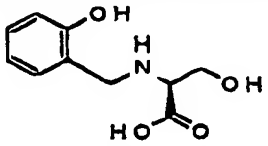
Moreover, on page 2, lines 17 to last line, Grams et al disclose that their compounds are a mimetic to cystine derivatives as an MMP inhibitor. Applicants submit that compounds that mimic MMP inhibitors are different from the suppressor of the activation of inflammatory factors in view of the site of activity. It should be noted that Grams et al only provide synthesis examples in the specification, and that there are no examples that measure the inhibitory effects of the compounds. Therefore, there is Grams et al fail to provide even an iota of expectation that their compounds are useful to mimic MMP inhibitors, much less suppress the activation of inflammatory factors.

Applicants also wish to note that an additional important aspect of the present invention is that the claimed compounds comprise an amine structure and the amine moiety may form an intra-molecular ring structure with 2-hydroxyl group on the aryl group, such that the compounds have a chelating activity (see Table 1, reproduced below). In contrast, the compounds exemplified by Grams et al are either amide-type or carbanoyl-type structures, which do not possess a chelating potential. Thus, it would be expected that these compounds provide distinct results from those obtained by the claimed compounds.

In fact, the present invention relates to a group of novel compounds that have an improved suppressing activity over known cystine derivatives as typically indicated in Table 1 of the specification.

Table 1

Test of potency of suppressing the activation of NF-κB

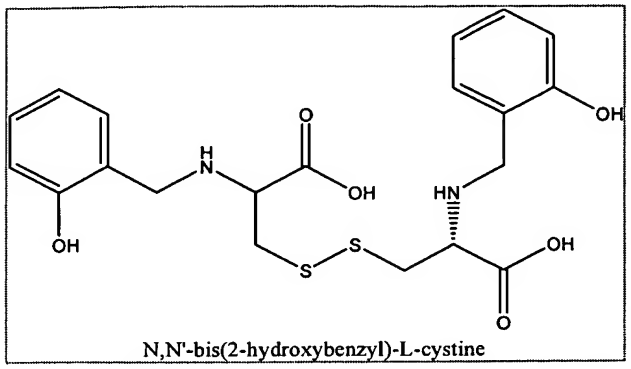
Test compound	Concentration (mM)	Suppression ratio (%)
	0.1 0.5 1.0	41 86 >100
N,N'-Bis(2-hydroxybenzyl)-L-cystine (inventive product)		
	10 30	48 67
N,N'-Diacetyl-L-cystine (control product)		
	10 30	17 34
N-(2-Hydroxybenzyl)-L-serine (control product)		

As shown in Table 1, the novel cystine derivative of the invention has the potency of suppressing the activation of NF-κB at the same level as or a higher level than that of N,N'-diacetyl-L-cystine or N-(2-hydroxybenzyl)-L-serine having been known to have the potency to suppress the activation of NF-κB. As such, the novel cystine derivative of the present invention has great potency of suppressing the activation of inflammatory factor. Such a result is neither disclosed or suggested by, and is not expected in view of, the disclosure of Grams et al.

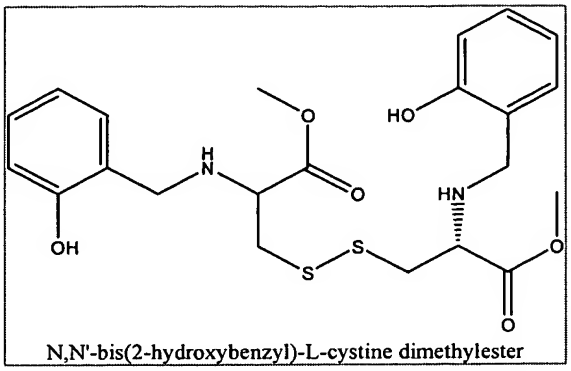
In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 7 and 20 under 35 U.S.C. §112, second paragraph, is respectfully traversed.

To address the Examiner's indefiniteness rejection, Applicants direct the Examiner's attention to the following structure of N,N'-bis(2-hydroxybenzyl)-L-cystine and the corresponding dimethyl ester:



N,N'-bis(2-hydroxybenzyl)-L-cystine



N,N'-bis(2-hydroxybenzyl)-L-cystine dimethylester

As should be readily apparent to the skilled artisan, N,N'-bis(2-hydroxybenzyl)-L-cystine only possesses two sites that are suitable for ester formation (corresponding to sites defined by X-R^2 and Y-R^3). In view of the foregoing, Applicants submit that Claims 7 and 20 are definite and that no amendment is believed to be necessary.

Applicants request withdrawal of this ground of rejection.

Finally, Applicants remind the Examiner that MPEP §821.04 states:

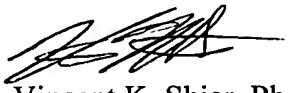
> "...if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined."

Accordingly, upon a finding of allowability of the elected product claims (Claims 1-20), withdrawn process claims (Claims 21-31) ***must*** be rejoined and subsequently examined. Acknowledgement to this effect is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Vincent K. Shier, Ph.D.
Registration No. 50,552

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)
NFO/VKS